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# Neurofibromatosis 1 and Osseous Fibrous Dysplasia in a Family

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**We report on the cosegregation of neurofibromatosis 1 (NF 1) and osseous fibrous dysplasia in a family. The father and 3 children by 2 women are affected. A fourth child had neither NF 1 nor osseous fibrous dysplasia.**

**All 4 affected individuals had NF 1, i.e., café-au-lait spots in 4, neurofibromata in 4, Lisch nodules in 3, macrocrania in 3, scoliosis in 2, and curvature of the long bones in 2. Each demonstrated various fibroosseous lesions of the skeleton including non-ossifying fibromas in 3 and both non-ossifying fibromas and fibrous dysplasia in one.**

**This pattern suggests that the fibrous bony lesions are a component of NF 1 in this family. Alternatively, a mutant gene resulting in the fibrous changes in bone could be linked to the gene for NF 1. Another possibility is the coincidence of the 2 non-linked traits segregating in the same family.** 

**KEY WORDS: fibrous dysplasia, neurofibromatosis 1, NF 1, non-ossifying fibroma, osseous fibrous dysplasia, pleiotropy, segregation**

## INTRODUCTION

We describe the occurrence in 4 relatives of two rare conditions. The first, neurofibromatosis 1 (NF 1), is a pleiotropic condition with autosomal dominant transmission. It is often associated with a variety of skeletal anomalies [Bahlin, 1978; Holt, 1978; Hunt and Pugh, 1961; Klatte et al., 1976]. The second condition, osseous fibrous dysplasia, refers to benign dysplastic bone formation in combination with a fibrous stroma. It includes several specific subtypes such as fibrous dysplasia, non-ossifying fibroma, and an aggressive form of osseous fibrous dysplasia (Table I). The occurrence of osseous fibrous dysplasia is reported to be sporadic.

There have been at least 8 reports of NF 1 and osseous fibrous dysplasia in individuals [Beggs et al., 1981; Erlemann et al., 1987; Fauré et al., 1986; Goodnough et al., 1975; Gross et al., 1989; Mandell et al., 1979; Rosenberg et al., 1967; Schwartz and Ramos, 1980]. However, a familial association has not been reported. We describe a father and 3 of his living children who have NF 1 and osseous fibrous dysplasia.

## CLINICAL REPORTS

We examined all the patients at the National Institutes of Health Interinstitute Genetics Clinic. Clinical and radiologic data are summarized in Table II. Family pedigree is shown in Figure 1.

### Patient 1: T.D. Pedigree III-26

The index case, T.D., weighed 3.72 kg at birth. Multiple café-au-lait spots were noted at birth. Motor and intellectual development were delayed. He walked 6 months after his peers and he did not use complete sentences until age 4. He did poorly in school, but completed 11 grades. Puberty began at age 13 years.

At 18 years, he enlisted in the Navy and passed a standard Navy physical examination. T.D. soon began to notice a dull ache in his left leg. It was non-radiating and there was no obvious difference in the temperature of the legs. He received a medical discharge from the Navy 8 months after enlistment. On radiologic exam, severe bilateral osseous fibrous dysplasia of the knees was noted. Multiple café-au-lait spots and subcutaneous nodules were noted, and the diagnosis of NF 1 was made.

Physical examination: height of 164, (4th centile), weight of 64 kg (60th centile), and a OFC of 57 cm (70th centile). Café-au-lait spots, axillary freckling, neurofibromata, and Lisch nodules were present on examination. He was otherwise normal except for tenderness of the left knee.

Radiographic evaluation included a complete skeletal survey and bone scintigraphy. Plain radiographs demonstrated bilateral, symmetrical lytic lesions of the distal femora and proximal tibiae (Fig. 2). The femoral

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TABLE I. Characteristics of Osseous Fibrous Dysplasia*

| Subtype | Age of onset | Location | Radiographic appearance | Histology | Natural history | Genetics |
|---|---|---|---|---|---|---|
| Non-ossifying fibroma | Childhood | Appendicular Metaphyseal | Small, eccentric lesions with scalloped borders | Fibrous Some giant cells Evidence of phagocytosis No bone formation | Spontaneous healing with skeletal maturity | Evans and Park report one family with 3 affected members—2 sibs and 1 offspring |
| Fibrous dysplasia | Childhood Adolescence | Flat bones Pelvis Knees Metaphyseal | Central, "ground glass" appearance | Fibrous "Fake trabeculae" (bone with no osteoblasts) Direct metaplasia Immature bone | Recurrence | No families reported-sporadic occurrence |
| Osseous fibrous dysplasia (aggressive type) | Childhood | Appendicular Metaphyseal Diaphyseal | Central, lytic, destructive | Active fibrous stroma Bone production (may have osteoblasts) Immature bone | Regressive Recurrence | No families reported-sporadic occurrence |

*[Bahlin, 1978; Evans and Park, 1978; Jaffe, 1958; Lichtenstein, 1972].

TABLE II. Summary of Clinical and Radiographic Data in 5 Cases

| | | Skin changes | | | Skeletal changes | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Case | Sex/Age | Café-au-lait spots | Lisch nodules | Neurofibromata | Macrocrania (percentile) | Scoliosis | Non-ossifying fibromas | Fibrous dysplasia | Curvature of tibia/fibula |
| T.D. propositus | M/19 | + | + | + | − (70%) | − | + | + Bilateral distal fibulae, proximal tibiae and fibulae | − |
| A.R. half-sib | F/16 | + | − | + | + (>95%) | + T-L scoliosis (7 degrees) | + | − | − |
| M.R. half-sib | M/14 | + | + | + | + (>99%) | + T-C scoliosis (5 degrees) | + | − | + Bilateral fibulae |
| J.R. half-sib | M/12 | − | − | − | − | − | − | − | − |
| H.R. father | M/42 | + | + | + | + (>97%) | − | + | − | + Bilateral fibulae |

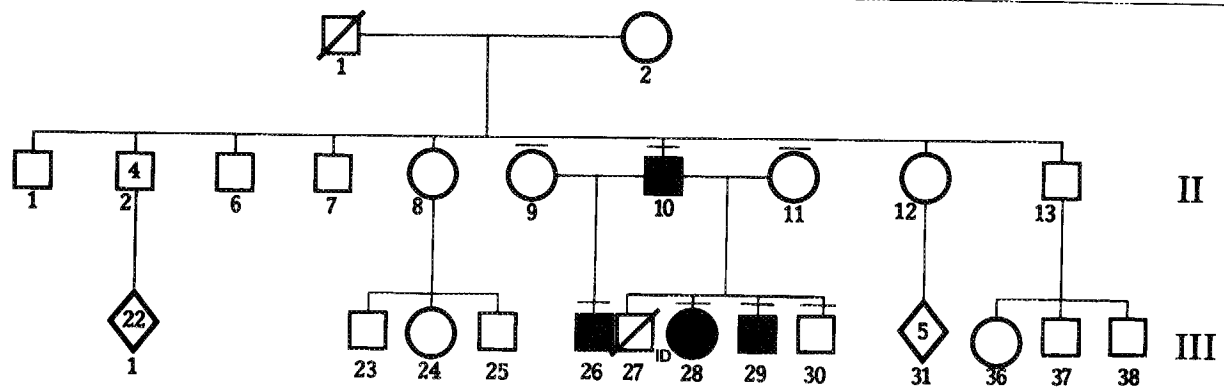


Fig. 1. Pedigree.

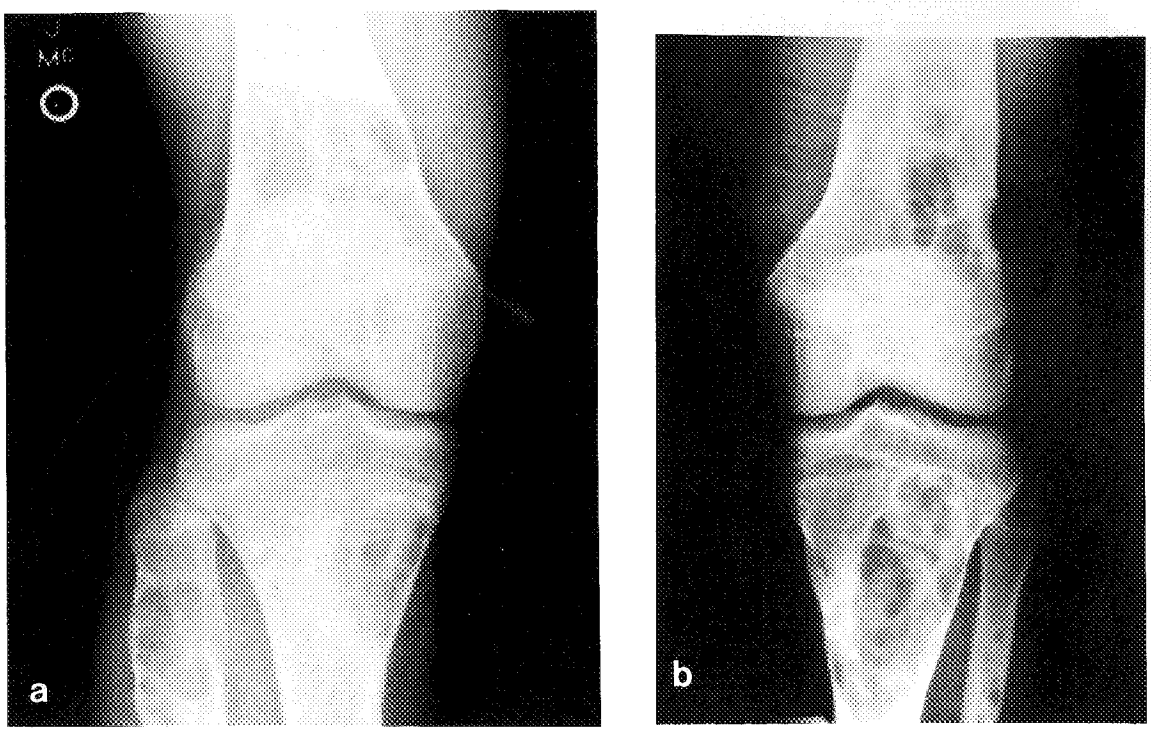


Fig. 2. Bilateral, symmetrical lesions of the distal femurs and proximal tibias of Patient 1.

lesions were metaphyseal with well-defined margins, sclerotic borders, and some cortical thinning. The left proximal tibia (symptomatic) lesion involved the entire metaphysis and epiphyseal portion, with "ballooning" of the cortex, and destruction of the subchondral bone. The contralateral tibia showed similar findings but with less destruction. The radiographic appearance suggested a benign process. No other radiographic abnormalities were noted. Bone scintigraphy showed increased uptake corresponding to the plain radiographs.

The bony defects of the left limb were treated in one stage by curettage and autogenous bone graft. At surgery, he had a large cystic cavity in the left tibia consisting of bloody fluid with an attenuated cortex and erosion of the adjacent subchondral bone. There was a thin fibrous lining of the cavity. Frozen section demonstrated benign fibrous tissue with multinucleated giant cells. This defect was reconstructed by segmental ipsilateral fibula bone grafts after thorough curettage. The distal femoral lesion was treated by curettage without bone grafts.

Post-operatively, the left limb was immobilized in a long-leg cast for 9 months until radiographs demonstrated graft incorporation. A long-leg brace was utilized for an additional 3 months.

Sections from the left femur curretings showed a lesion composed of spindle cells in interlacing bundles interspersed with giant cells. There were no neural elements. The diagnosis was a non-ossifying fibroma (Fig. 3).

A subcutaneous nodule was also examined histo-

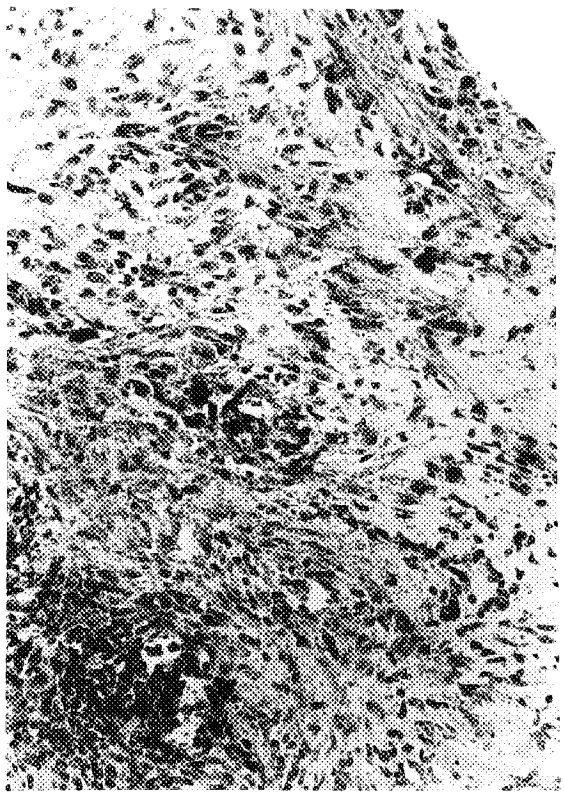

Fig. 3. A non-ossifying fibroma taken from the left femur curettings of Patient 1. The lesion is composed of spindle cells in interlacing bundles interspersed with giant cells. There are no neural elements.

logically. It showed a nerve trunk which had become markedly widened with Schwann cells and bundles of fibrous tissue in a loose stroma. The diagnosis was plexiform neurofibroma (Fig. 4).

### Patient 2: A.R. Pedigree III-28

A.R. is the 16-year-old half-sister of the index case. At age one, a biopsy proven subcutaneous neurofibroma was noted on her forehead. The nodule recurred as a disfiguring midline lesion despite several surgical procedures. Otherwise, she was in good health.

Physical examination: height of 168 cm (85th centile), weight of 49.9 kg (15th centile), and a OFC of 58 cm (>95th centile). A 3 × 5 cm, firm, biopsy proven neurofibroma extended from the forehead down to the bridge of the nose and the left upper eyelid. Three neurofibromata, multiple café-au-lait spots, and axillary freckling were present. Examination with a slit lamp did not show any Lisch nodules. Otherwise, she was normal on exam.

Plain radiographs showed a lobulated lesion in the distal shaft of the right femur, which is well circumscribed by osteosclerotic margins. The lesion originates from the inner aspect of the bony cortex and bulges within the cancellous bone and the medullary cavity of the distal femur. A similar, but smaller, lesion is seen in the distal metaphysis of the same femur (Fig. 5). Minimal scoliosis was seen in the thoraco-lumbar region. A lateral view of the skull showed a radiolucent bony defect in the parietal region. Bone scintigraphy showed increased uptake corresponding to the plain radiographs.

The forehead nodule was biopsied, and microscopic examination showed compactly arranged fusiform and oval cells within a fibrocollagenous matrix. Several large nerve branches were present within the tissue mass, and focal areas exhibited a plexiform pattern (Fig. 6). The diagnosis was neurofibroma.

### Patient 3: M.R. Pedigree III-29

M.R. is the 14-year-old brother of the previous patient and the half-brother of the index case. There were no complaints and past medical history was unremarkable.

Physical examination: height of 151 cm (12th centile), weight of 41.1 kg (5th centile), and a OFC of 59 cm (>99th centile). Multiple café-au-lait spots, a 2 × 4 cm neurofibroma, axillary freckling, and Lisch nodules were noted on examination. Findings on the remainder of the exam were within normal limits.

Plain radiographs demonstrated an oval radiolucent defect in the distal metaphysis of the left femur (Fig. 7) and increased cortical bone thickening in the distal shaft of the right fibula. There is deformity in the distal metaphysis of the right fibula. There is also a deformity in the trabecular pattern of the distal metaphysis of the right tibia. The fibulae are markedly bowed (Fig. 8). There is minimal scoliosis in the cervico-thoracic region.

Fig. 4. A plexiform neurofibroma from Patient 1. The nerve trunk is markedly widened with Schwann cells and bundles of fibrous tissue in a loose stroma.

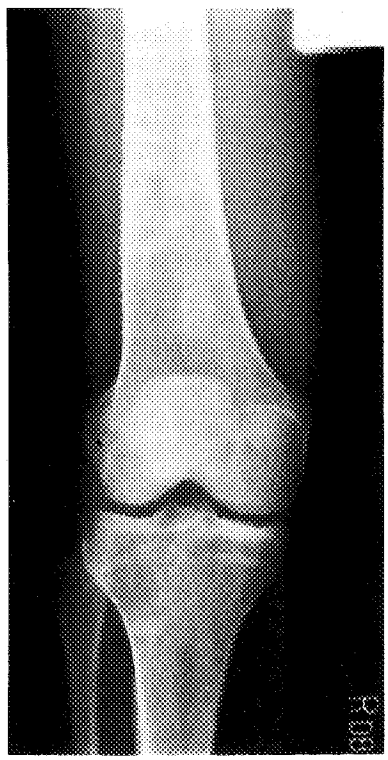

Fig. 5. A lobulated lesion in the distal shaft of the right femur and a similar, but smaller lesion in the distal metaphysis of the same femur of Patient 2.

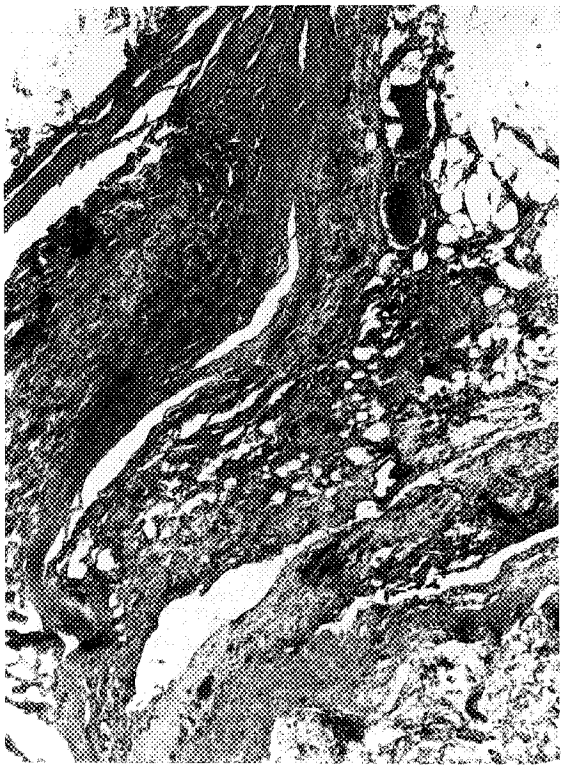

Fig. 6. A neurofibroma from Patient 2. Compactly arranged fusiform and oval cells are seen within a fibrocollagenous matrix. Several large nerve branches are present within the tissue mass and focal areas exhibit a plexiform pattern.

### Patient 4: J.R. Pedigree III-30

J.R. is the 12-year-old brother of the previous patient. There were no complaints and past history was unremarkable.

Physical examination was unremarkable. No café-au-lait spots were detected under either room light or Woods' light. No neurofibromata, Lisch nodules, axillary freckling, or skeletal anomalies were seen. Radiographs of the upper and lower limbs were unremarkable.

### Patient 5: H.R. Pedigree II-10

H.R. is the 42-year-old father of the previous 4 patients. He first noted neurofibromata on his abdomen at age 9 years. The number and size of his neurofibromata increased over time. At age 26, a large neurofibroma was removed from his right thigh. At age 37, six neurofibromata were removed from his face, neck, and abdomen due to pain or change in size.

Physical examination: height of 168 cm (15th centile), weight of 73 kg, and a OFC of 61 cm (>97th centile). Multiple café-au-lait spots, axillary freckling, greater than 100 neurofibromata, and 30–40 Lisch nodules were noted on exam. Otherwise, he was normal.

Plain radiographs demonstrated focal areas of increased density in the distal left femur and proximal right tibia (Fig. 9). The fibulae are bowed.

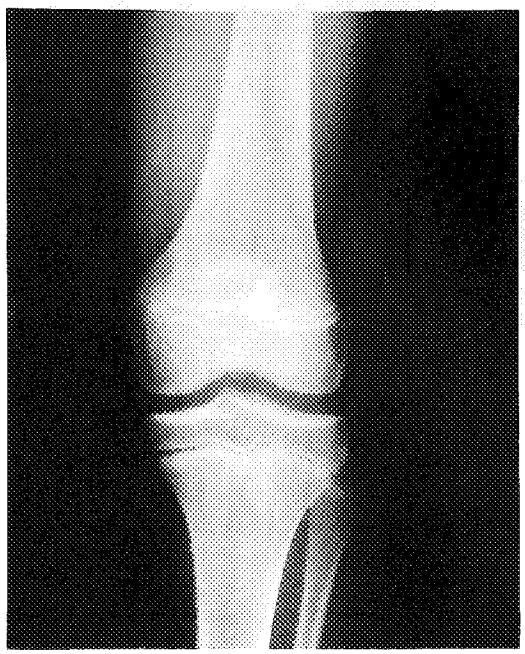

Fig. 7. An oval-shaped radiolucent defect in the distal metaphysis of the left distal femur in Patient 3.

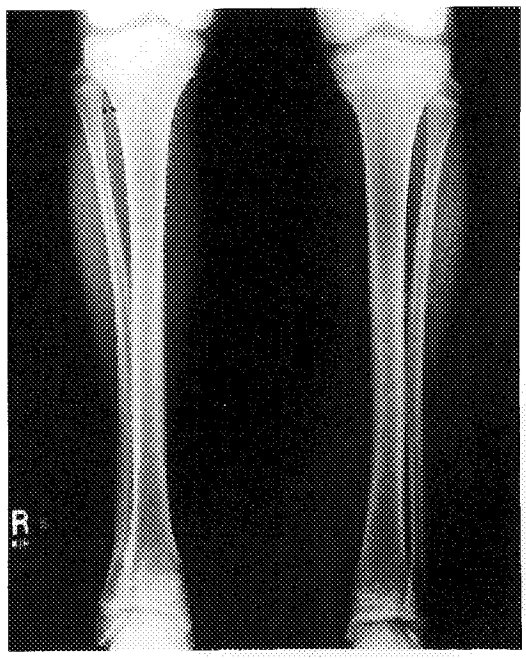


Fig. 8. The fibulae are markedly bowed in Patient 3.

### Family History (Pedigree–Fig. 1)

An infant son (III-27) of H.R. died at 3 months of sudden infant death. Family history failed to show any evidence of NF 1 or osseous fibrous dysplasia in H.R.'s

TABLE III. Reports of Neurofibromatosis 1 With Non-Ossifying Fibromas or Fibrous Dysplasia

| Author/year | Patient(s) | Diagnosis | Bone changes | Skin changes | Comments |
|---|---|---|---|---|---|
| Rosenberg et al. 1967 | 1 Family-mother and 9 siblings | Propositus-fibrous dysplasia | Fibrous dysplasia involving frontal bone and the floor of the anterior fossa. The roof of the right orbit was partially obscured and the proximal mandibular rami had an abnormal granular texture | At least 6 café-au-lait spots > 1.5 cm | |
| | | Mother-neurofibromatosis 1 | Scoliosis, irregular trabecular pattern of the mandible and granular lesions in the mandibular rami | Multiple neurofibromata and at least 6 café-au-lait spots > 1.5 cm | |
| | | 8 Siblings-neurofibromatosis 1 | Sibling 2-retarded ossification of anterior fontanel and a defect in the metopic suture<br>Siblings 4,5,6-cortical defects in the femur | 8 Siblings-at least 6 café-au-lait spots > 1.5 cm | |
| Goodnough et al. 1975 | 1 | Neurofibromatosis 1 with incidental non-ossifying fibroma | Non-ossifying fibroma in the right distal femur | Neurofibroma and multiple café-au-lait spots | |
| Mandell et al. 1979 | 38 | Neurofibromatosis 1 | 9 patients with bone changes-5 had multiple fibrocystic lesions, 4 had characteristic osseous lesions around the knees; vertebral scalloping and pedicle abnormalities were seen | All 9 of the patients with bone changes had 8 or more café-au-lait spots and neurofibromata | |
| Schwartz and Ramos 1980 | 1 | Neurofibromatosis 1 and multiple non-ossifying fibromas | Non-ossifying fibromas around knees and ankles, endosteal sclerosis of right femur, dysplastic thickening of the diaphysis, lumbar scoliosis, and hypoplasia of the right iliac crest | Plexiform neurofibromas | |

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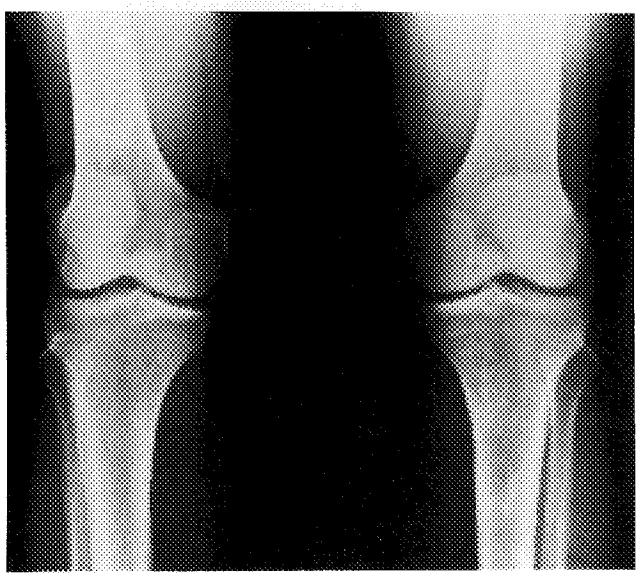

Fig. 9. Focal areas of increased density in the distal left femur and proximal right tibia of Patient 5.

parents, 10 sibs, and the 35 nephews and nieces with whom he had contact. This strongly suggests that H.R. represents a new mutation that arose in the germ line of his 32-year-old nonconsanguineous parents.

## DISCUSSION

To our knowledge, there have been no previous reports of NF 1 with osseous fibrous dysplasia occurring in multiple family members. Jaffe remarked that a patient with lesions of disseminated non-ossifying fibroma and patches of brownish skin pigmentation, but without neurofibromata, could be interpreted as an instance of neurofibromatosis dominated by bone lesions—an abortive form, or forme fruste, of neurofibromatosis [Jaffe, 1958]. Since that time, a number of individuals have been reported with both NF 1 and osseous fibrous dysplasia (Table III). Fauré et al. reported the occurrence of NF 1 with non-ossifying fibromas in 4 patients, 2 of whom were sisters [Fauré et al., 1986]. This is not an obvious case of NF 1 in Patient 4. She initially presented with a left suprarenal neuroblastoma with bone metastases. She later developed growth hormone insuffi-

TABLE III. (continued)

| Author/year | Patient(s) | Diagnosis | Bone changes | Skin changes | Comments |
|---|---|---|---|---|---|
| Beggs et al. 1981 | 1 | Neurofibromatosis 1 non-ossifying fibroma, and coarctation of the aortic arch | Multiple lesions at the ends of the shafts of the distal femorae, tibiae, and fibulae (non-ossifying fibromas) | Multiple café-au-lait spots and neurofibromata | |
| Fauré et al. 1985 | 4 | | | | |
| | Patient 1 | Neurofibromatosis 1 and non-ossifying fibroma | Large non-ossifying fibromas of both femurs and the left tibia | Numerous café-au-lait spots and 2 neurofibromas | |
| | Patient 2 | Neurofibromatosis 1 and "fibrous bone defects" | Severe scoliosis; congenital pseudarthrosis of the right forearm, numerous fibrous defects of bone including the right clavicle, humerus, radius, both fibulae, and the right upper tibial metaphysis | Multiple café-au-lait spots | |
| | Patient 3 | Neurofibromatosis 1 and non-ossifying fibroma | Large non-ossifying fibromas of upper tibial and fibular metaphyses | Multiple café-au-lait spots | |
| | Patient 4 (sister of Patient 3) | Non-ossifying fibroma | Non-ossifying fibromas of both femurs tibiae, fibulae, and right humerus | None | Patient initially presented with a left suprarenal neuroblastoma with bone metastases. She also had growth hormone insufficiency and precocious puberty. This does not clearly represent an instance of neurofibromatosis in this patient. |
| Erlemann et al. 1987 | 3 | Neurofibromatosis 1 and non-ossifying fibroma | Multiple osteolytic lesions with sclerotic margins | ——— | |
| Gross et al. 1989 | 1 | Neurofibromatosis 1 and non-ossifying fibroma | Multiple lytic lesions in the distal aspect of both femurs and proximal portion of the right tibia, "ribbon rib" deformity of the right 10th–12th ribs, hypoplasia of the pedicles of the 12th thoracic and 1st lumbar vertebrae | Multiple café-au-lait spots, axillary freckling, bilateral Lisch nodules | |
| Schotland et al. | 1 Family | Neurofibromatosis 1 and osseous fibrous dysplasia | Multiple lesions at the ends of the shafts of the distal femorae and in the tibiae and fibulae, bowing of the fibulae, mild scoliosis, macrocrania | Multiple café-au-lait spots, neurofibromata, axillary freckling, Lisch modules | |

ciency, precocious puberty, and non-ossifying fibromas. In fact, the patient's findings have some overlap with Albright syndrome [Riccardi, 1987]. Goodnough et al. (1975) thought that the relationship of non-ossifying fibromas to neurofibromatosis was coincidental. Mandell et al. [1979] however, thought that when multiple fibrocystic lesions are present around the knee, the diagnosis of neurofibromatosis should be considered and a biopsy is unnecessary. Schwartz and Ramos [1980] called non-ossifying fibromas another phenotypic manifestation of the mesodermal abnormalities in neurofibromatosis. Rosenberg et al. [1967] and Campanacci et al. [1983] also proposed that there may be a relationship between the 2 diseases.

There is a striking parallel between NF 1 and Jaffe-Campanacci syndrome [Mirra et al., 1982; Campanacci et al., 1983]. This syndrome is characterized by café-au-lait spots and multiple non-ossifying fibromas and is often associated with mental retardation. It differs from NF 1 in that, to our knowledge, neurofibromata have not

been described in patients with Jaffe-Campanacci syndrome, and in addition, a heritable basis has not been established. Jaffe's description above of a patient with disseminated non-ossifying fibromas and patches of brownish skin pigmentation has been cited as the first description of Jaffe-Campanacci syndrome.

Molecular studies first showed the locus of the NF 1 gene on chromosome 17 [Barker et al., 1987; Seizinger et al., 1987] and more recently, the gene has been cloned [Cawthon et al., 1990; Viskochil et al., 1990]. It would be of interest to perform molecular studies on this family to determine if the association of NF 1 and osseous fibrous dysplasia represents: (1) a particular mutation in the NF 1 gene with an atypical clinical phenotype, (2) a deletion or rearrangement which disrupts the NF 1 gene and a neighboring gene whose defect results in osseous fibrous dysplasia, (3) a mutation in a novel gene whose defect results in both disease, and (4) coincidence, although highly unlikely, is another possibility.

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